Review article

J. Perinat. Med.
4 (1976) 59

Current concepts of reproductive immuno-biology

W. G. Smith, A. E. Beer

During the past ten years, there has been a great deal of progress in elucidating the **essential immunogenetic prerequisites necessary for the primary take or healing in of the blastocyst on the uterine bed**, the cellular interactions with its bed, the development of the resultant fetal organismic graft, and its ultimate and prompt repudiation at term. Contrary to various hypotheses that have been advanced as to the immunologic non-reactivity of the mother during gestation, **females do become immunologically cognizant of the presence in their uteri of genetically alien fetuses. The human conceptus** by virtue of its inherited paternal antigens **fulfills the definition of an allograft** and predicting from all other known graft behavior, should be rejected. Coeval with the evolution of viviparity, Nature has had to solve the problem of nourishing the embryo within the uterus, a paradoxical situation which seems to defy the known laws of transplantation biology. The resultant immunological interrelationships between mother and offspring have been the object of intense research, the results of which demonstrate both beneficial and harmful effects related to the maternal-fetal symbiotic relationship.

Immunology intrudes into nearly every aspect of mammalian reproduction and affords an important means of analyzing or monitoring several of its components. **Choriocarcionoma**, a relatively uncommon tumor in Caucasians has commanded an entirely disporportionate amount of attention in terms of the literature and conference time devoted to it, as much because it is a **highly successful fetal maternal allograft**, as because of its relatively high rate of spontaneous regression, and susceptibility to chemotherapy. However, the most significant advances in understanding the immunological aspects of choriocarcinoma will come from investigations into the immunological relationship between a mother and her normal conceptus.

Mammalian reproductive activity involves a sequence of events that is of particular interest to transplantation and reproduction biologists alike. **The antigen challenge begins with the repeated innoculation of the adult female via the intravaginal route with hundreds of millions of highly specialized, motile and short lived spermatozoa,** suspended in the complex media of seminal plasma. Following fertilization and at some time in its subsequent development, **the zygote must necessarily express paternally inherited transplantation**

Curriculum vitae

WILLIAM GARY SMITH, *born January 11, 1942. 1964 University of Western Ontario, Bachelor of Arts. 1964–1968 University of Western Ontario, Doctor of Medicine. 1968–1969 rotating Internship, Victoria Hospital, London Ontario Canada. 1969–1970 Junior Assistant Resident, Victoria Hospital, London Ontario Canada. Canada, Obstetrics and Gynecology. 1970–1971 Junior Assistant Resident, St. Joseph's Hospital London, Ontario 6 months Medicine and 6 months Surgery. 1971–1972 Perinatal Research, McMaster University, Hamilton Ontario. 1972–1973 Chief Resident, Obstetrics and Gynecology, Victoria Hospital, London, Ontario. 1973 Teaching Fellow, Obstetrics and Gynecology, Victoria Hospital, London, Ontario (University of Western Ontario).*

antigens that are alien to its mother. In the absence of special dispensations and on purely genetic grounds mothers would be expected to reject their fetuses.

1 Female response to the antigens of semen

Spermatozoa express tissue specific [41, 47, 62, 82, 99], **male specific** [8, 55, 59] **blood group** [20, 31, 37], **and histocompatibility antigens** [32, 34, 38, 95]. Since the initial work by LANDSTEINER [63] and METCHNIKOFF [70], the distinctive immunological properties found in the components of the male ejaculate have been considered to contribute to **harmful sensitization phenomena** [88] and apart from the possibility of **explaining some cases of infertility**, these phenomena have been used to effect the **development of an immunological means of fertility control** [15].

It has been demonstrated that after a long course of intraperitoneal injections of syngeneic or allogeneic spermatozoa [68], female mice may develop high titers of sperm agglutinins. Although maturation and ovulation occurred normally in such sensitized females, spermatozoa did not appear to reach the site of fertilization in adequate numbers leading to a lowered rate of fertilization and a reduction in litter size [16].

KATSH [54] has found that **antibodies to seminal components** are persistently detectable in the serum and cervical mucous of certain patients with **idiopathic sterility**. However, attempts involving the co-operation of prostitutes and other volunteers to relate the magnitude of antibody response to the degree of coital exposure to seminal material have been unsuccessful. Recently, BEHRMAN [14] has shown that a significant decrease in antibody titers can be obtained with occlusive (condom) therapy and that 50–60% of these hitherto sterile patients will subsequently conceive.

Currently, one of the greatest problems in assessing the data relating to **immunological tests of infertility**, is the lack of correlation of the various results (Tab. I) [9]. BOETTCHER [21] has recently presented cogent evidence which indicates that **the sperm agglutinating activity in the sera of both pregnancy and virgin women may be due to a lipoprotein-steroid conjugate rather than immunoglobulins.** At this point in time, it would seem that the relatively simple and easy to perform **post-coital test** [46, 90] **will provide the information necessary to rule out immunological phenomena as a factor in individuals with infertility of undetermined etiology.**

Recently it has been shown that washed allogeneic spermatozoa injected directly into the uterine

Tab. I. Comparing various tests used to detect antibodies to human spermatozoa in serum, seminal plasma or cervical mucus and the correlation of their results with infertility

Comments about tests	Macroscopic agglutination (KIBRICK)	Immobilization	Microagglutination (FRANKLIN-DUKES)	Immunofluorescence
Antibodies dected	IgG	IgG and IgM	None	IgG and IgM
Antigens responsible	Cell surface	Lactoferrin-sperm coating antigen	None	Sperm tail, acrosome, equatorial segment and post nuclear cap
Complement dependent	No	Yes	No	No
Correlation with sterility in females	35%	18%	38%	Unknown
Positive response in controls	40%	0%	46%	Unknown
Correlation with sterility in males	3.3%	Unknown	Unknown	Unknown
Correlation with other tests	None	None	None	None

lumen of inbred strains of rats, mice and hamsters are able to sensitize the host systemically, as evidenced by hypertrophy of the lymph nodes draining the uterus and a subsequent accelerated rejection time of skin grafts bearing similar histocompatibility antigens [8]. The fact that **repeated normal matings do not elicit sensitization on the part of female hosts** hints that eigher the numbers of sperm gaining entrance to the uterus at any one time remains a subthreshold stimulus or that these cells are cleared very rapidly from this organ following intercourse.

To date, there have been few attempts to study the immunological activity of physiological uterotubal secretions of subjects immunized primarily by the intra-uterine route. However, the uterine endometrium of most higher mammals is abundantly endowed with lymphatics and seems to have all the pre-requisites necessary to deliver either antigen or antigen primed immunologically competent cells of hematologic origin to a draining lymph node [69]. Diffuse deposits of lymphoid cells beneath the endometrium may be triggered to provide antibody (probably IgA) locally which may be transported across the mucous membrane and into the lumen [5, 56]. However, **local production of antibody at the uterine level against seminal antigens is minimal** when serum antibody levels in the same individual are taken into consideration.

Local innoculation of the uterus with spermatozoa is also able to elicit an immunological reaction characteristic of **delayed hypersensitivity**. When the uterus is rechallenged with genetically identical spermatozoa, a fulminant reaction characterized by edema, dilation, and vascular congestion of the uterus occurs. This reaction subsides and the organ reassumes its normal appearance both to outward inspection and histological examination within four days [10]. The striking uterine response cannot be evoked by challenge innoculation of the sensitized female by any other route. This phenomena is probably related to **host immunologic memory cells that persist within the uterine mucosa and stroma** [107]. Since phagocytosis of sperm occurs more actively in a sensitized uterus [66], one might expect that the resultant reproductive performance of the sensitized uterus would be impaired if females with locally sensitized uteri were mated with allogeneic males against whose tissue antigens this sensitization was directed. This is not the case as evidenced by increased number and weights of subsequent offspring gestated in the sensitized uterus [10]. That this is an immunological phenomena is attested by the finding that reproductive performance was not enhanced in those situations in which conceptuses involved were genetically compatible with their mother. Considering the evidence that epididymal spermatozoa are antigenically more effective when innoculated into the uterus as compared to other innoculation sites, and that the timing of the nodal proliferative change coincides with blastocyst implantation, it is tempting to speculate that **the maternal immunological response to alien spermatozoa is beneficial in securing tenure for the implanting blastocyst** [33]. Currently, there is a tremendous interest in the **immunological approach to contraception by vaccination using spermatozoa as antigen** [42], however, the enhanced reproductive performance of the locally sensitized uterus casts doubt on the tenability of such a concept.

2 The uterus as an immunologically privileged site

There are certain sites in the body which are known as immunologically privileged sites [18]. These include the **brain** and the **anterior chamber of the eye**. In these unique anatomical locations, tissue allografts can be grafted and once vascularized, they survive for anomalously long periods of time seemingly exempt from immunological rejection. Immunologically privileged sites can be created surgically in rodents simply by excising a circular island of skin from its underlying connective tissue in such a way that a narrow central umbilical cord of connective tissue containing an artery and vein but no lymphatic vessels, is preserved to nourish the uprooted skin flap [4]. The privileged status of the artifically created site turns upon the lack of afferent lymphatic pathways that connect with regional lymph nodes and convey antigenic material to a seat of immunologic response. **For many years, there has been a suspicion that the uterus might be an immunologically privileged site.** Tumor allografts are promptly rejected [85] but since some

of these grafts might have invaded beyond the physiologic boundaries of the uterine endometrium and entered adjacent tissue, it was impossible to deny a privileged status to the uterus on the basis of these experiments. It was subsequently demonstrated that allografts of normal non-invasive tissue [79] transplanted to the uterus under similar conditions were consistently rejected. However, **neither of the experimental conceptuses incited a typical decidual response** [57].

To investigate the possibility that the uterus might under certain circumstances be a privileged site, required the introduction of tissue or cellular allografts as model conceptuses into the intact uterine lumen. Small skin grafts or suspensions of skin epidermal cells introduced into the uterine lumen healed in consistently and very rapidly on the untraumatized endometrium provided that the endometrium was in the proliferative phase and the host animal had not ovulated. Contrary to expectation, no decidual response was elicited in the uterus [7]. In this anatomically unnatural site, genetically compatible grafts of skin or skin cells survived indefinitely but when the intra-uterine skin grafts were from genetically alien donors, they incited and succumbed to typical allograft reactions, surviving no longer than they would have done if transplanted orthotopically. Under conditions of the grafting described, **the non-pregnant uterus affords no more hospitality to a skin allograft than does a conventional site prepared in the integument.** If host female rats are in the **pre-implantation stage of pregnancy**, or are made **pseudo-pregnant** by appropriate mechanical stimulation of the cervix [26] at the time of insertion of skin allografts into their uteri, typical decidual responses consistently develop beneath these grafts. Under these experimental conditions, **the survival of the skin allografts was significantly prolonged** [8]. The possibility that the increased life span resulted from a non-specific hormonally mediated suppression of the host's response was refuted by the observation that skin allografts transplanted to conventional sites on pregnant or pseudo-pregnant hosts were rejected with normal promptitude. Unlike the situation with primary or first set skin allografts in immunological virgin hosts, decidual tissue afforded no protection whatever to intrauterine skin allografts placed in the uterus of specifically pre-sensitized hosts.

These findings are consistent with the conclusion that **decidual tissue subadjacent to the alien skin graft in non-immune subjects affords a partial blockage of the afferent lymphatic vessels.** This blockade may prevent foreign antigenic material from reaching the proximal seat of the immunological response in the host i.e. the regional paraaortic lymph nodes, or it may interrupt the passage of peripherally sensitized maternal lymphocytes to these organs. Another possibility is that this lymphatic obstruction facilitates the presentation of fetal antigenic material by the intra-venous route which is known to favor the development of enhancing or blocking antibodies capable of frustrating both the development and the expression of cellular immunity [81].

3 Elicitation and expression of immunity in the uterus

When allografts are transplanted to most sites in the body, or suspensions of allogeneic cells are injected into tissues, there soon follows hypertrophy and proliferation of the regional lymph nodes draining the graft site. This is an indicator that immunologically competent cells within these organs have been stimulated by alloantigens of the graft and that these stimulated cells engage in proliferative and other events that underlie the immune response [18].

As with spermatozoa, when skin allografts or suspensions of allogeneic epidermal cells are innoculated directly into the uterine cavity they incite a very significant enlargement of the lymph nodes draining this organ as well as a state of transplantation immunity in the host [24]. This suggests that **these draining lymph nodes are the main site of the host's reactivity against the intra-uterine graft** and that antigenic material in the uterine cavity is able to cross its endometrial lining and enter the primary lymphatic channels of this organ...

Once implantation of a blastocyst has occurred, the invasive potential of the trophoblast allows intimate exposure of alien paternally derived antigens ot maternal tissues. Just as antigenic recognition of foreign skin grafts is manifested by regional lymph

node hypertrophy, maternal recognition of foreign antigens present on the fetal placental unit also incites proliferative and hypertrophic changes within the paraaortic lymph nodes [80]. Syngeneic pregnancies bearing genetically similar fetuses to their mothers do not produce significant changes within these nodes. The only reasonable interpretation of these findings is that **tissue alloantigens of fetal origin find their way into the draining maternal uterine lymphatics and stimulate the lymph node enlargement** [93].

Allogeneic fetuses despite their ability to stimulate the regional lymph nodes do not increase the host's resistance to test tissue allografts: Indeed they seem to weaken it [8, 10, 17, 93]. This is thought to be due to their ability to evoke the formation of humoral antibodies corresponding to the major unshared histocompatibility determinants of their progeny. **During pregnancy, suppressive factors possibly blocking antibodies** [40, 94], **are produced in the paraaortic lymph nodes and interfere with the expression of maternal cellular reactivity.** Acting in a manner analogous to Rh immune globulin (anti-D) [35], they may fulfill an important immunoregulatory role in **ensuring survival to term of Nature's most successful allograft.**

Whatever the significance, these responses have no adverse effect on the fetus. Indeed, there is evidence that they may even be beneficial to its development.

The above findings indicate that the uterus is

a) a **very efficient route for the initiation of transplantation immunity** both by solid tissue allografts as well as by monodisperse suspensions of cells and
b) **able to express a state of immunity as effectively as any other site in the body.**

Paradoxially, the immunologically alien feto-placental unit in this environment is completely undaunted. Its success most likely reflects the capacity of the trophoblast to function as an antigenically neutral buffer zone on behalf of the fetus, preventing host lymphocytes from engaging with fetal tissues in a manner that will lead to transplantation immunity, as well as preventing lymphocyte effector cells from a sensitized female from harming vulnerable fetal cells at the level of the placenta. It has been shown that there is a tendency for **increased numbers of implantations with increasing histoincompatibility between the mother and her fetuses** [12, 59, 101]. Long term genetic studies of brother and sister matings of inbred strains of rats reveal that there is a selective elimination of homozygotes either pre or post-natally [24, 74] and this might well reflect an important naturally occurring phenomena among wild populations to assure the survival of excess numbers of heterozygotes [59, 105].

4 Histoincompatibility and maternal immune status as determinants of the size of the feto-placental unit

In 1964, BILLINGTON [19] observed that the offsping of mice differing at the important genetic H2 locus had significantly heavier placentas than did homozygous fetuses of either parental strain. Comparison of the size of placentas from intra-strain matings with those which developed when fertilized eggs from such matings were transferred to the uteri of AgB locus incompatible surrogate mothers, reinforced the selective advantage of histoincompatibility. These observations were subsequently confirmed by several investigators [48, 49, 73]. **The immune status of the mother with regard to the alien tissue antigens of her fetus is an important determinant of placental size and growth of the fetus.** In mothers presensitized against the tissue antigens of her hybrid fetus, the placentas were significantly larger than in similar gestations by normal mothers. Furthermore, the placentas of similar F_1 hybrid fetuses borne by mothers which had been rendered tolerant of their fetal antigens were significantly smaller [12].

In man, JONES [51], carried out analysis of maternal ABO blood groups and placenta weights, recognizing that the presence of these antigens on the trophoblast was in doubt [106]. The results obtained suggested that disparity between fetus and mother with respect to these antigens was associated with relatively smaller placentas. A recent report by JENKINS [50], relates placental weight in the human to histo-compatibility antigen dependent reactivity between the maternal and fetal cells and suggests that **histoincompatibility does influence**

placental weight in humans and greater disparity is associated with larger placentas.

If maternal reactivity against fetal tissue histocompatibility antigens in part determines the weight of the fetal-placental units, then the draining para-aortic lymph nodes and/or the spleen either singularly or together might be the most likely generator of the pertinent effector cellular or humoral responses contributing to this phenomena. To elucidate the influence of these two lymphoid organs, females had either their bilateral paraaortic nodes or their spleens removed prior to mating. Both procedures significantly reduced the mean weights of the fetal-placental units [12]. Since the spleen is the principal seat of the synthesis of antibodies when antigenic material is presented via the intravenous route [83], it seemed likely that humoral antibodies might be the principal mediators of placenta and fetal growth in utero. Further support for these antibody mediators is gained by the ability to passively transfer enhanced reproductive performance with hyperimmune serum raised against paternal antigens [12].

5 Maternal fetal exchange of cells and its consequences

Although anastomoses never develop between the blood circulations of mother and their fetuses even at the capillary level, it is well known that **the placenta does not constitute a cell impermeable membrane.** The opportunity for exchange of cells is greater in species with hemochorial placentas than in species in which maternal and fetal circulations are heavily insulated from one another. Fetal lymphocytes, red blood cells and up to one-half million trophoblast cells a day constantly enter the maternal circulation [60, 84, 86, 98]. In vivo, the majority of trophoblast cells probably undergo enzymatic degradation in the maternal blood stream. However, a small proportion are filtered out intact in the capillary bed of the lungs where they gradually disappear unaccompanied by any detectable host response. The apparent inability of these ectopic allografts of synctio-trophoblast to proliferate and form benign metastases probably reflects their highly differentiated and terminal cell status. Whether this normal physiologic process of feto-maternal deportation of trophoblast fragments has any functional significance is an unresolved question.

The problems of transplacental fetal to maternal passage of genetically dissimilar red blood cells are well known to obstetricians [1, 2, 65].

6 Maternal leukocyte isoimmunization and its consequences

The formation of isoagglutinins to leukocytes after multiple transfusions has been well documented. It has been established that leukocyte agglutinins may appear in the maternal serum following multiple pregnancies [76, 77, 102]. According to PAYNE, the antibodies are present in the sera of about 25% of women who have had more than three pregnancies. These findings afford additional evidence of both the occurence and the incidence of fetal-maternal transmission of leukocytes since the antigens concerned are not present on erythrocytes [58]. Since multiparous women can only form antibodies against the leukocyte antigens transmitted to their fetuses by their husbands and absent in themselves, then antibodies are necessarily of limited specificity, sometimes being capable of recognizing a single antigen. Such individuals are an excellent source of sera for histocompatibility testing since most of the serologically detectable antigenic determinants, referred to as leukocyte antigens are in fact, histocompatibility antigens. These isoantibodies persist at relatively high titers in the sera of multiparous women for many years after their last progeny.

Few of the infants born of leukocyte sensitized mothers have manifested clinical evidence of any damaging influence. However, in a retrospective study, TERASAKI [96] obtained suggestive data that women with HL-A (human leukocyte antigen) antibodies give birth to a significantly higher proportion of infants with congenital anomalies than women without these antibodies. These investigators postulated that antibodies produced by mothers against the HL-A antigens of fetuses have an adverse effect on fetuses in subsequent pregnancies.

Isoimmunization of mothers to platelet antigens through blood transfusion or natural transplacental

transfusion with fetal platelets during pregnancy also occurs. The antiplatelet antibodies produced by these perfectly normal mothers readily cross the placenta and may destroy fetal platelets. Pregnancy in women with Idiopathic Thrombocytopenia results in a transient platelet deficiency in the newborn infant as a consequence of transfer of the anti-platelet antibodies across the placenta [44].

7 Maternal of fetal transfer of leukocytes

The passage of cells across the placenta is not one way. There is evidence of a **covert exchange of cells from the mother to the fetus** [27, 29, 75, 104]. One of the consequences of a **significant number of immunologically competent maternal cells entering the fetus and attacking the foreign antigenic sites is runt disease**, a syndrome characterized by diarrhea, dermatitis, wasting and death. In the rat, it is easy to incur runt disease by innoculation of the pregnant female during pregnancy with lymphocytes that are able to recognize the fetus as foreign [9, 13]. These antigen reactive cells cross the placenta and attack the fetus. Close scrutiny of infants who fail to thrive and who also present symptoms resembling those of experimentally procurred runt disease in animals, has produced a few cases of natural maternally induced runt disease, some even documented by evidence of lymphocyte chimerism [52, 100]. It is also possible that a significant proportion of the fetuses that die in utero of unknown causes have also been the victims of infiltration by their mother's lymphocytes. The fetus may be protected in the majority of cases by the transplacental passage of blocking antibodies raised during pregnancy and secondly, by their ability to react immunologically against many kinds of antigen. The maturation of immuno-competence in the normally sterile environment in which the fetus develops may reflect a protective mechanism which can normally take care of relatively small numbers of potentially harmful immunocompetent maternal lymphocytes [3, 36, 89]. Indeed, **maternal lymphocytes may be the first pathogens to which a fetus is normally exposed.** It is significant that **in most cases of established or suspected maternally induced runting in man, there was evidence of a congenital immunodeficiency disease in the infant** which would have provided the maternal immunocytes the security of tenure needed for them to mount effective reactions against their hosts.

8 Graft versus host disease and lymphomas

In 1959, two radiologists KAPLAN and SMITHERS drew attention to the marked similarity between the abnormalities of animals suffering from experimentally induced runt disease and those of patients affected by certain lymphomas or malignancies of lymphoid tissue [53]. Subsequently it has been shown that mild or even subclinical graft versus host disease in both mice and rats increases the incidence of lymphomas. Recently SCHWARTZ and his associates have shown that these tumors may arise through the unmasking of latent oncogenic viruses in host cells by subclinical graft versus host disease that may have been initiated by trans-placentally passaged lymphocytes during the preceeding gestation [87].

9 Immunological consequences of breast feeding

Just as maternal to fetal transfer of lymphoid cells across the placenta could have severe immunological consequences for the immature and genetically alien fetus, it appears that **maternal milk serves as a transporting medium by which viable immunocompetent leukocytes gain access to the nursing infant.** In appropriate circumstances, these cells are capable of expressing both immunogenicity and immunocompetence in the neonatal host. Moreover, the demonstrable immunologic consequences of milk-borne cells in the nursing offspring are similar to those seen in animals exposed in utero to alien cells [39].

The nutritional value of a mother's milk has always been accepted as part of the natural scheme of infant care. Cells long known to be present in milk have not received much attention nor have had any importance attached to them. Only with the advent of the commercial dairy industry early in the twentieth century under the watchful eye of public health officials did serious research on milk cells begin and centered primarily around sanitary implications. Most of these early studies focused

on the origin and characterization of bovine milk cells and whether or not they might be indicators of pathological conditions [23, 43, 45, 103]. The most conspicuous cells reported, termed **colostral corpuscles**, were very large nucleate cells containing cytoplasmic fat droplets [67]. In addition to colostral corpuscles and **epithelial cells**, the early investigators described cells such as **polymorphonuclear neutrophils**, small and large **lymphocytes** and occasionally **eosinophils**. It has recently been shown that the colostral corpuscles are actually fat-engorged **macrophages** [92]. Colostral cell counts are normally higher (1.5–4.1 million cells per cc) than those of milk, which average 1.5 million cells per cc [72]. Ninety per-cent of the total colostral mononuclear cell population in human milk has been identified as macrophages and the remaining 10% are lymphocytes [92]. Recently it has been reported that **50% of these lymphocytes are thymus influenced cells or T cells** and **22–42% are B cells bearing surface immunoglobulin** [28]. Various immunological parameters of these cells have been tested [72, 91] and it appears that they exhibit normal immunological reactivity in vitro. Contrary to the findings of DIAZ-JOUANEN and WILLIAMS, we have found the milk lymphocytes to be responsive to the plant mitogen PHA.

However, there is a wide variation in the daily milk cell numbers and by the tenth day post partem, it is very difficult to isolate large numbers of cells.

The fate of the ingested milk cells has not fully been resolved, yet data in the laboratory rat model suggests that **the cells do cross the gut and confront neonatal tissues resulting in altered immunological reactivity of the recipient** [11]. Maternal milk borne cells must endure the process of ingestion if they are to reach neonatal tissues in a viable form. The high buffering capacity of the milk itself due to the large protein moiety may be important in this regard. The precise site or mode of transepithelial cell passage in the neonatal rat gut is currently unknown. However, several investigators have presented evidence that cells in other species are capable of penetrating the gastro-intestinal epithelium [30, 61].

Nursing represents a **natural transplantation of immunocompetent cells to the suckling infant.** This adoptive immunization may be an immunologically important aspect of infant care among mammalian species. It has long been known that young mammals are provided with an endowment of humoral antibodies from their mother to protect them during early infancy against certain pathogens confronting them in their new environment [11]. Dependent upon the species, **animals can be passively immunized with protective antibodies via the placenta, the milk or both** [22]. It would seem logical that the protective responsibility of the mother would also include the transfer of immunologically competent cells along with antibodies to her progeny. Yet transplacental cell traffic from the mother to an immunologically immature fetus is quite hazardous, often resulting in acute graft versus host disease in the offspring [6]. Milk serving as a transport medium would provide the neonate with a population of immuno-competent cells at a time when the infant is more mature and better able to cope with an alien cellular inoculum. **A normal function of the mammary gland may be to provide the infant with transient cellular immune protection an undertaking too dangerous to be performed by the placenta.** MOHR [71], has recently shown that transient but specific cellular immunity as manifested by tuberculin sensitivity is imparted to the nursing human infant. Recently PITT [78], using a rat model of necrotizing enterocolitis induced by Klebsiella demonstrated another facet of the protective benefit provided to the nursing neonate. Necrotizing enterocolitis an often fatal disease characterized by exfoliation of the intestinal mucosa, primarily occurs in premature human infants maintained by formula feeding. PITT and her colleagues found that breast feeding protected young rats against necrotizing entercolitis, whereas the affected infants receiving only formula or breast milk, treated to kill viable cells, succumbed to the disease. In addition, cells separated from rat breast milk killed 99% of Klebsiella organisms in vitro but accellular breast milk was totally ineffective.

It is important to consider that in addition to transmission of **viable cells** in some species maternal cellular immunological benefits could be provided to the neonate by **subcellular components from immune leukocytes** such as **Transfer factor** [64] or

immune RNA [97]. A subcellular endowment might be particularly applicable to human infants whose stomach contents become extremely acidic within a few hours after birth. However, the possibility that milk borne cells are protected in some manner from the low pH and proteolytic enzymes of the stomach and thereby survive even in the human infant's digestive system cannot be disregarded especially in view of the very high buffering capacity of milk.

That **breast feeding** not only furnishes sustenance but also is a **means of providing cellular immunity to the infant** is an intriguing hypothesis which is slowly gaining experimental support.

10 Conclusion

Immunobiology of reproduction has to date, lacked quantitative data needed to resolve many of the here-to-fore unexplained and controversial phenomena related to gestation. Until the early 1960's, the gestating female was felt to be relatively immunologically non-responsive during pregnancy. It is only in the last ten years that the problem of surreptitious immunological reactivity of the pregnant female has been addressed, and as the science of immunobiology incorporates with more sophisticated in vitro technology, many of the dichotomies related to maternal fetal immunological coexistence will be answered.

Keywords: Blocking antibodies, breast feeding, fetal immunology, foreign antigens, graft versus host reactions, immunocompetence, lymphocytes, maternal immunological reactivity, suppressive factors, transplantation biology.

Zusammenfassung

Derzeitige Vorstellungen über die Immunbiologie der Fortpflanzung.

Die feto-maternale symbiotische Zusammengehörigkeit während der Schwangerschaft scheint die bekannten Gesetze der Transplantationsbiologie zu widerlegen, denn der Fetus sollte aufgrund seiner vorgegebenen väterlichen Antigenität aus immunologischen Gründen abgestoßen werden. Daß dies nicht der Fall ist, zeugt für eine **spezielle Situation, die während der Schwangerschaft herrscht.** Die durch die Schwangerschaft induzierte immunologische Interkorrelation beginnt mit dem Coitus. **Schon die Spermatozonen weisen Antigenität auf** und sind im Experiment in der Lage, in der Gebärmutter eine fulminante Überempfindlichkeitsreaktion hervorzurufen, die ihrerseits in der Lage ist, im Fortpflanzungsgeschehen die Blastozystenimplantation zu begünstigen. **Die Gebärmutter ist immunologisch kein bevorzugtes Organ;** die durch die Schwangerschaft hervorgerufene deziduale Reaktion könnte jedoch einen relativen immunologischen Schutz für die implantierende Blastocyste ermöglichen, indem das Angebot von Fremdantigenen über den intravenösen Weg „gesammelt" wird, was bekanntlich die Entwicklung von blockierenden Antikörpern begünstigt.

Der Hauptsitz der mütterlichen immunologischen Reaktion auf Fremdantigene, die in den fetalen Geweben anwesend sind, spielt sich in den paraaortalen Lymphknoten ab, die den schwangeren Uterus versorgen. Während der Schwangerschaft werden suppressive Faktoren, möglicherweise blockierende Antikörper in den paraaortalen Lymphknoten gebildet. Diese beeinflussen die zelluläre Reaktivität der Mutter. Diese Antikörper wirken ganz ähnlich wie das Rh-Immunglobulin und könnten eine **wichtige immunoregulatorische Funktion** bei der Gewährleistung des fetalen Lebens bis zum Termin erfüllen. Die mütterliche immunologische Reaktion gegenüber den fetalen gewebeinhaerenten Histokompatibilitätsantigenen bestimmt teilweise das Gewicht der **feto-plazentaren Einheit.** Ein Antigenaustausch zwischen Mutter und Fetus findet regelmäßig in beiden Richtungen statt und betrifft rote Blutkörperchen, Plättchen, Leukozyten und Trophoblastzellen. Eine der Konsequenzen des feto-maternalen Leukozytenaustausches ist die **„graft versus host"-Erkrankung,** welche das lymphatische System für gewisse Lymphome und maligne Erkrankungen prädisponieren könnte. Ein feto-maternaler zellulärer Austausch könnte auch während der **Stillperiode** stattfinden; unter geeigneten Umständen sind diese Zellen in der Lage, sowohl **Immunokompetenz beim Neugeborenen** hervorzurufen. In der Muttermilch wurden sowohl T- wie B-Lymphozyten isoliert, wenngleich die tägliche Zellanzahl stark variiert. In Abhängigkeit von der Gattung können Neugeborene passiv mit schützenden Antikörpern via Muttermilch immunisiert werden und die schützende Verantwortlichkeit der Mutter könnte auch den Transfer von **immunologisch kompetenten Lymphozyten mit der Muttermilch** einschließen. Diese Lymphozyten wären in der Lage, einen vorübergehenden immunologischen Schutz zu vermitteln.

Schlüsselwörter: Blockierende Antikörper, fetale Immunologie, Fremdantikörper, „graft versus host"-Reaktion, Immunokompetenz, mütterliche immunologische Reaktivität, Lymphozyten, Stillen mit Muttermilch, Transplantationsbiologie.

Résumé

Concepts courants de l'immuno-biologie de reproduction

Durant la grossesse, les relations **symbiotiques** materno-foetales défient les lois connues de la biologie de transplantation et, en vertu de ses antigènes paternels hérités, **le foetus devrait être immunologiquement rejeté.** Qu'il n'en soit pas ainsi est le fait évident qu'il existe des **situations spéciales durant la grossesse.** Les inter-relations immunologiques provoquées en gestation commencent au coit. **Les spermatozoides se comportent comme des antigènes** et peuvent expérimentalement produire dans l'utérus une réaction d'hypersensitivité très importante, capable d'accroître l'activité reproductrice sous forme d'implantation de blastocytes. **L'utérus n'est pas un siège immunologique privilégié,** mais la réaction temporaire suscitée par la grossesse peut assurer une protection immunologique relative pour la formation blastocystaire en fixant la présence d'antigènes étrangers par la voie intraveineuse dont on sait qu'elle favorise le développement d'anticorps inhibiteurs.

Le principal siège de la réactivité immunologique maternelle aux antigènes étrangers présents sur le tissus foetal se trouve dans les noeuds lymphatiques para aortiques qui irriguent l'utérus gravide. Durant la grossesse, des facteurs suppressifs, probablement anticorps inhibitifs, sont produits dans les noeuds lymphatiques para aortiques et interfèrent avec la réactivité cellulaire maternelle. Ces anticorps agissent d'une manière analogue à l'immunoglobuline Rh et peuvent remplir un **rôle immunorégulateur** important en assurant la survie jusqu'au terme. La réactivité immunologique maternelle envers les antigènes histocompatibles des tissus foetaux détermine partiellement le poids de **l'unité placentaire foetale.** L'échange antigénique entre la mère et le foetus a lieu selon le processus habituel avec échange bidirectionnel de cellules rouges, de plaquettes, de leucocytes et de throphoblaste. L'une des conséquences des échanges de leucocytes de la mère au foetus est **la maladie du «graft versus host»** qui peut prédisposer à certains lymphomes et malignités du système lymphoïde.

Les échanges cellulaires de la mère au foetus peuvent aussi se produire durant **l'allaitement** et dans des conditions appropriées; ces cellules sont capables de manifester à la fois une **immunogénicité et une immunocompétence dans l'hôte néonatal.** Les lymphocytes T et B ont été isolés du lait maternel bien qu'il y ait une grande variation dans le nombre des cellules journalières. Selon les espèces, les bébés peuvent être immunisés passivement avec des **anticorps** protecteurs durant l'allaitement, et la responsabilité protectrice de la mère peut aussi inclure le **transfert par le lait de lymphocytes immunologiquement compétents** et capables d'assurer une immunoprotection transitoire.

Mots-clés: Allaitement, antigènes étrangers, ancitorps inhibiteurs, biologie transplantatoire, facteurs suppressifs, immunocompétence, immunologie foetale, lymphocytes, réactions du «graft versus host», réactivité immunologique maternelle.

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Dr. W. G. Smith
Anderson Hospital and
Tumor Institute
Houston, Texas 77025/
USA